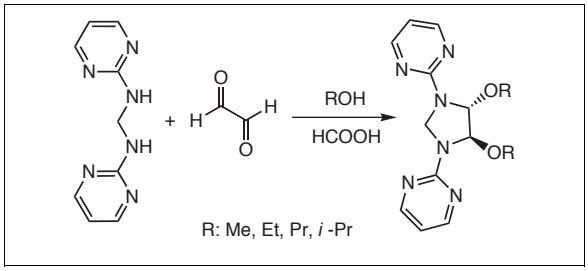
One-Pot Stereoselective Synthesis of *trans*-4,5-Dialkoxy-1,3-bis (2-pyrimidinyl)imidazolidines Through a Three-Component Reaction

Mehdi Ghandi*, Farshid Salimi and Abolfazl Olyaei

School of Chemistry, University College of Science, University of Tehran, Tehran, Iran
Fax No. +98 21 66404848 E-mail: ghandi@khayam.ut.ac.ir

Received August 31, 2005



Stoichiometric reaction of 2-aminopyrimidine with formaldehyde in the presence of formic acid catalyst in water gave *N,N'*-bis(2-pyrimidinyl)methanediamine (**5**). Subsequent cyclocondensation of **5** with glyoxal in alcohol (MeOH, EtOH, PrOH and *i*-PrOH) under reflux conditions led to the formation of the corresponding 4,5-dialkoxy-1,3-bis(2-pyrimidinyl)imidazolidines (**6a-d**). 4,5-Dihydroxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6e**) was obtained when the reaction was carried out in acetonitrile. Based on ^{1}H NMR analysis, it was found that the *trans*-dialkoxyimidazolidines (**6**) were selectively obtained in these cyclocondensation reactions.

J. Heterocyclic Chem., **43**, 791 (2006).

Introduction.

Reaction of diamides and diamines with aqueous glyoxal has been the subject of several investigations [1-11]. In 1962, Vail and co-workers reported the reaction of various bisamides of the type RCONH-X-NHCOR (X = alkylene or substituted alkylene) with glyoxal to produce the desired cyclic compounds [1]. In the case of diamines, most of the reports have been limited to ethylenediamine and its derivatives [2-3]. Willer has reported the reaction of *N,N'*-dibenzylethylenediamine with glyoxal in ethanol giving a mixture of three crystalline products **1**-**3** (Figure 1) [3].

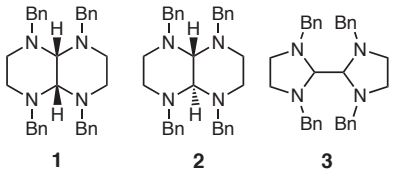


Figure 1

There have been a few reports of the reactions between *gem*-diamines and glyoxal. Koppes described the reaction of hexafluorodiaminopropane with glyoxal which led to the formation of 3,3,7,7-tetrakis(trifluoromethyl)-2,4,6,8-tetraazabicyclo[3.3.0]octane **4**. In this reaction, 4,5-dihydroxy-2,2-bis(trifluoromethyl)imidazolidine could not be isolated (Figure 2) [4].

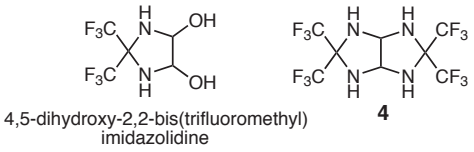


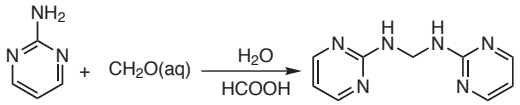
Figure 2

Imidazolidines are important building blocks in biologically active compounds, and carriers of pharmacologically active carbonyl compounds [12-15]. In this paper, we wish to report the solvent mediated stereoselective three-component reaction of *N,N'*-bis(2-pyrimidinyl)methanediamine (**5**) with glyoxal in alcohol (MeOH, EtOH, PrOH and *i*-PrOH) which afforded the new substituted imidazolidine compounds. Such a three-component reaction using *gem*-diamines has not been yet reported. The stereochemistry of the products will be assigned based on ^{1}H NMR spectroscopy.

Results and Discussion.

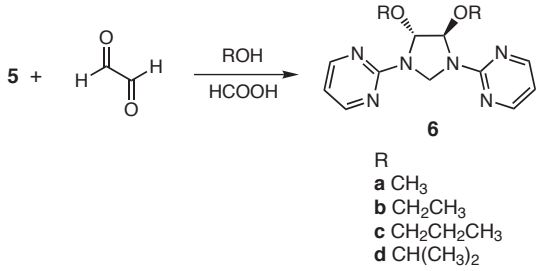
Condensation of 2-aminopyrimidine (2 mol) with aqueous formaldehyde in the presence of aqueous formic acid catalyst in water at room temperature gave *N,N'*-bis(2-pyrimidinyl)methanediamine (**5**) as a white precipitate in 87% yield, as previously described (Scheme 1) [16]. It was found that using water as solvent in comparison with other solvents such as acetonitrile or alcohol afforded the highest yield.

Scheme 1



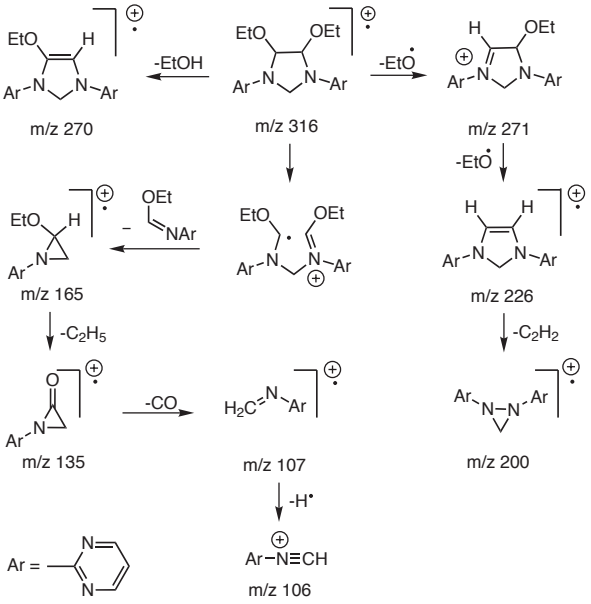
Cyclocondensation of compound **5** with aqueous glyoxal in alcohol (MeOH, EtOH, PrOH and *i*-PrOH) at reflux conditions in the presence of formic acid catalyst afforded the white precipitates of 4,5-dialkoxy-1,3-bis(2-pyrimidinyl)imidazolidines (**6a-d**) (Scheme 2).

Scheme 2



When the reaction was carried out in acetonitrile, *trans*-4,5-dihydroxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6e**) was obtained as the unique product. Reaction of compound **6e** with acetic anhydride in the presence of H_2SO_4 resulted in the formation of the corresponding *trans*-4,5-diacetoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6f**) (Scheme 3).

Scheme 4



Identification of products **6a-f** was made by elemental analyses, mass spectra and NMR spectroscopy. Yields, melting points and elemental analyses are presented in Table 1.

With the exception of **6f**, compounds **6a-f** exhibited the parent ions with medium intensity. Ion fragmentation of compound **6b** is depicted in Scheme 4 as the representative common features of the parent ion decomposition.

Scheme 3

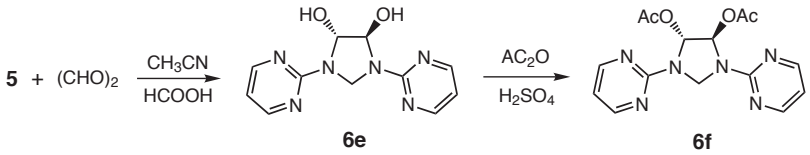


Table 1

Yields, melting points and elemental analyses of compounds **6a-f**.

	R	Mp (°C)	Yield (%)	Elemental Analysis Calcd. (Found)		
				C	H	N
6a	Me	200-202	50	54.16 (53.96)	5.55 (5.59)	29.16 (29.01)
6b	Et	135-137	55	56.96 (56.82)	6.33 (6.40)	26.58 (26.41)
6c	Pr	110-112	75	59.30 (59.15)	6.97 (7.10)	24.42 (24.63)
6d	*i*-Pr	145-147	68	59.30 (59.39)	6.97 (7.10)	24.42 (24.38)
6e	H	212-214	85	50.77 (50.51)	4.61 (4.76)	32.30 (32.11)
6f	Ac	200-202	50	52.32 (52.41)	4.65 (4.70)	24.42 (24.31)

The ^{1}H NMR spectra of compounds **6a-f** showed a sharp singlet for the methylene group localized at δ values between 5.08 and 5.68 ppm in agreement with a *trans* configuration, whereas, methylene signal would appear as an AB quartet spin system if the substituents at the positions 4 and 5 of the imidazolidine ring were *cis* to each other [11]. Methine moiety appeared as a singlet signal in **6a-d** and **6f**. In the case of **6e**, methine and hydroxyl protons exhibited an AB quartet spin system. Upon addition of D_2O into NMR sample, the hydroxyl signal disappeared and the signal of methine moiety collapsed into a singlet. In ^{1}H NMR spectrum of compound **6d**, the methyl groups of each isopropyl moiety appeared as two doublets at δ 1.17 and 1.29 ppm.

Two intense signals were also observed in ^{13}C NMR spectrum at δ 22.37 and 22.81 ppm consistent with the diastereotopicity of methyl groups. The IR spectra of compounds **6a-f** did not exhibit peaks due to NH, OH or CO, except for **6e** and **6f** which showed OH and CO stretch absorptions at 3276 and 1753 cm^{-1}, respectively, with a relatively high intensity.

In summary, the general reaction described here presents a novel cyclocondensation of *N,N'*-bis(2-pyrimidinyl)methanediamine (**5**) with glyoxal in alcohol leading to the formation of *trans*- 4,5-dialkoxy-1,3-bis(2-pyrimidinyl)imidazolidines (**6a-d**). This is an example of stereoselective solvent mediated ring formation of immidazolidines.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker AC-80P and DRX-500 AVANCE spectrometers. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass analyses of the products were conducted with a HP (Agilent technologies) 5937 Mass selective Detector. Elemental analyses were carried out with a Thermo Finningan (FLASH 1112 SERIES EA) CHNS-O analyzer.

General Procedure for the Preparation of 4,5-Dialkoxy-1,3-bis(2-pyrimidinyl)imidazolidines (**6a-d**).

To a suspension of compound **5** (0.3 g, 1.48 mmol) in alcohol (MeOH, EtOH, PrOH or *i*-PrOH) (10 mL), were slowly added formic acid (0.02 g of 98% aqueous solution, 0.44 mmol) and glyoxal (0.20 g of 40% aqueous solution, 1.48 mmol). The reaction mixture was stirred at reflux for 20 hours. The solvent was evaporated under reduced pressure. Water (5 mL) was added to the residue and the solid formed was filtered, washed with cold water and dried. The crude product was recrystallized from EtOH-H_2O (1:1).

4,5-Dimethoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6a**).

White crystals (50%), mp 200-202 °C; ^{1}H nmr (DMSO-d_6, 80 MHz): δ 3.46 (s, 6H, 2 x *CH*$_3$), 5.18 (s, 2H, *CH*$_2$), 5.68 (s, 2H, *CH*), 6.81 (t, 2H, *J* = 4.8 Hz , 2 x pyrimidine H-5), 8.50 (d, 4H, *J* = 4.8 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr (DMSO-d_6, 20 MHz): δ 55.78, 62.49, 90.16, 112.57, 158.41, 160.07; ms (relative intensity %): m/z 288 (M$^+$, 5), 258 (48), 226 (12), 152 (91), 107 (16), 88 (100).

Anal. Calcd. for $C_{13}H_{16}N_6O_2$: C, 54.16; H, 5.55; N, 29.16. Found: C, 53.96; H, 5.59; N, 29.01.

4,5-Diethoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6b**).

White crystals (55%), mp 135-137 ºC; ^{1}H nmr ($CDCl_3$, 80 MHz): δ 1.19 (t, 6H, *J* = 7.2 Hz, 2 x *CH*$_3$), 3.62 (q, 4H, *J* = 7.2 Hz, 2 x *CH*$_2$CH$_3$), 5.37 (s, 2H, *CH*$_2$), 5.84 (s, 2H, 2 x *CH*), 6.65 (t, 2H, *J* = 4.8 Hz, 2 x pyrimidine H-5), 8.38 (d, 4H, *J* = 4.8 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr ($CDCl_3$, 20 MHz): δ 16.06, 64.23, 71.74, 88.97, 112.63, 158.50, 160.34; ms (relative intensity %): m/z 316 (M$^+$, 37), 271 (100), 270 (75), 226 (24), 165 (85), 135 (36), 107 (10).

Anal. Calcd. for $C_{15}H_{20}N_6O_2$: C, 56.96; H, 6.33; N, 26.58. Found: C, 56.82; H, 6.40; N, 26.41.

4,5-Dipropoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6c**).

White crystals (75%), mp 110-112 ºC; ^{1}H nmr ($CDCl_3$, 500 MHz): δ 0.90 (t, 6H, *J* = 7.4 Hz, 2 x *CH*$_3$), 1.57-1.68 (m, 4H, 2 x CH$_2$*CH*$_2$CH$_3$), 3.65 (t, 4H, *J* = 6.7 Hz, 2 x O*CH*$_2$), 5.42 (s, 2H, *CH*$_2$), 5.87 (s, 2H, 2 x *CH*), 6.72 (t, 2H, *J* = 4.7 Hz, 2 x pyrimidine H-5), 8.43 (d, 4H, *J* = 4.7 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr ($CDCl_3$, 125 MHz): δ 11.22, 23.75, 62.79, 70.51, 90.21, 112.60, 158.50, 160.41; ms (relative intensity %): m/z 344 (M$^+$, 50), 286 (100), 226 (42), 200 (8), 179 (74).

Anal. Calcd. for $C_{17}H_{24}N_6O_2$: C, 59.30; H, 6.97; N, 24.42. Found: C, 59.15; H, 7.10; N, 24.63.

4,5-Di-*i*-propoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6d**).

White crystals (68%), mp 145-147 ºC; ^{1}H nmr ($CDCl_3$, 500 MHz): δ 1.17 (d, 6H, *J* = 6.2 Hz, 2 x *CH*$_3$), 1.29 (d, 6H, *J* = 6.1 Hz, 2 x *CH*$_3$), 4.08-4.15 (m, 2H, 2 x *CH*(CH$_3$)$_2$), 5.39 (s, 2H, *CH*$_2$), 5.84 (s, 2H, 2 x *CH*), 6.69 (t, 2H, *J* = 4.7 Hz, 2 x pyrimidine H-5), 8.41 (d, 4H, *J* = 4.7 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr ($CDCl_3$, 125 MHz): δ 22.37, 22.81, 61.46, 69.55, 88.68, 111.89, 157.82, 159.83; ms (relative intensity %): m/z 344 (M$^+$, 18), 286 (46), 226 (31), 178 (93), 108 (100).

Anal. Calcd. for $C_{17}H_{24}N_6O_2$: C, 59.30; H, 6.97; N, 24.42. Found: C, 59.39; H, 7.10; N, 24.38.

4,5-Dihydroxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6e**).

To a suspension of **5** (0.3 g, 1.48 mmol) in acetonitrile (10 mL), were slowly added formic acid (0.02 g of 98% aqueous solution, 0.44 mmol) and glyoxal (0.2 g of 40% aqueous solution, 1.48 mmol). After refluxing for 15 hours, the mixture was cooled and filtered. The precipitate was washed with cold acetonitrile to give **6e**. Recrystallization from DMSO-EtOH (1:1) gave white pure crystals of **6e** in yield 85%, mp 212-214 ºC; ^{1}H nmr (DMSO-d_6, 500 MHz): δ 5.08 (s, 2H, *CH*$_2$), 5.73 (d, 2H, *J* = 5.8 Hz, 2 x *CH*), 6.17 (d, 2H, *J* = 5.8 Hz, 2 x *OH*), 6.84 (t, 2H, *J* = 4.8 Hz, 2 x pyrimidine H-5), 8.48 (d, 4H, *J* = 4.8 Hz, 2 x pyrimidine H-4/6); ^{1}H nmr (DMSO-d_6 + D_2O): δ 5.07 (s, 2H, *CH*$_2$), 5.68 (s, 2H, 2 x ring

CH), 6.83 (t, 2H, *J* = 4.8 Hz, 2 x pyrimidine H-5), 8.43 (d, 4H, *J* = 4.8 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr (DMSO-d_6, 125 MHz): δ 61.86, 86.36, 112.80, 158.98, 159.56; ir (potassium bromide) 3276 (OH) cm^{-1}; ms (relative intensity %): m/z 260 (M^+, 19), 242 (10), 200 (100).

Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.77; H, 4.61; N, 32.30. Found: C, 50.51; H, 4.76; N, 32.11.

4,5-Diacetoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**6f**).

A stirred solution of **6e** (0.15 g, 0.57 mmol) in acetic anhydride (10 mL) containing one drop of concentrated H_2SO_4 was heated at 40-50 ºC. After 1.5 hours, the solution was evaporated under vacuum at 50 ºC. The residue was triturated with cold water, filtered and dried to give **6f** in yield 50%, mp 200-202 ºC; ^{1}H nmr ($CDCl_3$, 500 MHz): δ 2.08 (s, 6H, 2 x CH_3), 5.41 (s, 2H, CH_2), 6.70-6.82 (t, 2H, *J* = 4.8 Hz, 2 x pyrimidine H-5), 7.04 (s, 2H, 2 x *CH*), 8.43 (d, 4H, *J* = 4.8 Hz, 2 x pyrimidine H-4/6); ^{13}C nmr ($CDCl_3$, 125 MHz): δ 21.40, 62.92, 84.25, 113.52, 158.55, 158.70, 169.89; ir (potassium bromide) 1753 (CO) cm^{-1}; ms (relative intensity %): m/z 343 (M-1, 5), 285 (80), 225 (95), 201 (55), 136 (65), 108 (100), 79 (70), 43 (63).

Anal. Calcd. for $C_{15}H_{16}N_6O_4$: C, 52.32; H, 4.65; N, 24.42; O, 18.60. Found: C, 52.41; H, 4.70; N, 24.31; O, 18.68.

Acknowledgement.

The authors wish to thank the research council of the University of Tehran for financial support.

REFERENCES AND NOTES

[1] S. L. Vail, C. M. Moran, H. B. Moor, R. M. H. Kullman, *J. Org. Chem.*, **27**, 2071-2074 (1962).

[2] A. Alexakis, J-P. Tranchier, N. Lensen, P. Mangeney, *J. Am. Chem. Soc.*, **117**, 10767-10768 (1995).

[3] R. L. Willer, D. W. Moore, D. J. Vanderah, *J. Org. Chem.*, **50**, 2365-2368 (1985).

[4] W. M. Koppes, M. Chaykovsky, H. J. Adolph, R. D. Gilardi, C. F. George, *J. Org. Chem.*, **52**, 1113-1119 (1987).

[5] I. J. Ferguson, A. R. Katritzky, R. Patel, *J. Chem. Soc., Perkin Trans. 2*, 1564-1567 (1976).

[6] W. R. Dunnavant, F. L. James, *J. Am. Chem. Soc.*, **78**, 2740-2743 (1956).

[7] J. Nematollah, R. Ketcham, *J. Org. Chem.*, **28**, 2378-2380 (1963).

[8] J. G. Frick, R. G. Harper, *Ind. Eng. Chem. Prod. Res. Dev.*, **21**, 599-600 (1982).

[9] L. A. Cort, N. R. Francis, *J. Chem. Soc.*, 2799-2801 (1964).

[10] R. L. Willer, D. W. Moore, C. K. Lowe-Ma, D. J. Vanderah, *J. Org. Chem.*, **50**, 2368-2372 (1985).

[11] A. T. Nielsen, R. A. Nissan, A. P. Chafin, R. D. Gilardi, C. F. George, *J. Org. Chem.*, **57**, 6756-6759 (1992).

[12] V. Sharma, C. L. Crankshaw, D. Piwnica-Worms, *J. Med. Chem.*, **39**, 3483-3490 (1996).

[13] C. R. Sage, M. D. Michelitsch, T. J. Stout, D. Biermann, R. Nissen, J. Finer-Moore, R. M. Stroud, *Biochemistry,* **37**, 13893-13901 (1998).

[14] G. Crank, D. R. K. Harding, S. S. Szinai, *J. Med. Chem.,* **13**, 1212-1215 (1970).

[15] G. Crank, D. R. K. Harding, S. S. Szinai, *J. Med. Chem.,* **13**, 1215-1217 (1970).

[16] B. Skowronska-Serafinowa, *Roczniki Chem.,* **29**, 932-933 (1955).